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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/775,204	02/11/2004	Craig A. Rosen	PF564	1797

22195 7590 07/13/2005

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EXAMINER	
WAX, ROBERT A	

ART UNIT	PAPER NUMBER
1653	

DATE MAILED: 07/13/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/775,204	ROSEN ET AL.	
	Examiner	Art Unit	
	Robert A. Wax	1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 April 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *22-45* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *22-45* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *11 February 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *04262005, 05262005*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Information Disclosure Statement

1. The information disclosure statements filed April 26, 2005 and May 26, 2005 have been considered. Please see the attached initialed PTO-1449s.

Inventorship

2. In view of the papers filed April 26, 2005, it has been found that this nonprovisional application, as filed, through error and without deceptive intent, improperly set forth the inventorship, and accordingly, this application has been corrected in compliance with 37 CFR 1.48(a). The inventorship of this application has been changed by adding Steven M. Ruben as an inventor, thus resulting in an inventive entity at the time of filing of Craig A. Rosen, William A. Haseltine, David J. Ballance, Andrew J. Turner and Steven M. Ruben.

3. In view of the papers filed April 26, 2005, the inventorship in this nonprovisional application has been changed by the deletion of David J. Ballance and Andrew J. Turner. Thus, the corrected inventive entity is Craig A. Rosen, William A. Haseltine and Steven M. Ruben.

The application will be forwarded to the Office of Initial Patent Examination (OIPE) for issuance of a corrected filing receipt, and correction of Office records to reflect the inventorship as corrected.

Response to Arguments

4. Applicant's arguments, filed April 26, 2005, have been fully considered and are persuasive. Specifically, with regard to the enablement rejections made under 35 USC, 112, first paragraph, the evidence is such that indicates that it would not require undue experimentation to make fragments and variants of albumin that have the claimed properties in view of the amount of knowledge about albumin. Furthermore, the evidence is such that it would not require undue experimentation to make fragments and variants of GLP-1 that retain GLP-1 activity in view of the vast amount of knowledge about GLP-1 fragments and variants. In addition, a rejection under written description is not warranted since there is enough structure-function relationship for both proteins to place the claimed invention in possession of the public; again, due to the vast amount of knowledge about both proteins. However, upon further consideration, a new ground of rejection is made below under 35 USC 103(a). Any rejection not expressly repeated below is hereby withdrawn. Examiner notes that claim 45 to the method of treatment of diabetes does not include administration of the composition of claim 44.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made..

6. The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

7. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 22-45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Becquart et al. (EP 0 413 622) in view of Fleer et al. (US Patent 5,876,966), Yamamoto et al. (US Patent 5,506,120) and Bridon et al. (US Patent 6,514,500).

Becquart et al. teach fusion proteins of albumin with therapeutic proteins. That this increases the serum half-life of the therapeutic protein is taught at page 2, lines 23-30. Attention is also directed to Example 10 where they demonstrate that an albumin-CD4 fusion protein "allows a significant increase in the stability of CD4" and the "CD4 moiety of the HAS-CD4 hybrid apparently retains an active conformation." They also teach bivalent hybrid protein complexes of the structure CD4-HSA-CD4 and expression of the fusion proteins in yeast. They do not teach GLP-1 as the therapeutic protein, nor do they teach arrangement of the multiple copies of the therapeutic protein in a tandem arrangement.

Fleer et al. teach fusion polypeptides between therapeutic proteins and albumin exhibiting enhanced shelf life and serum half-life. The fusions may be made with the therapeutic protein at the C-terminal of albumin or at the N-terminal or one copy at each end of the albumin molecule (see Fig 1A-C and Examples 1-3). Increased in vitro activity is taught for von Willebrand factor fusions with albumin at column 22, lines 25-30; this implies that the fused vWF would also inherently have increased in vivo activity. The preferred host cell in which to make the fusion proteins is yeast (instant claims 37-40), claim 11 teaches expression in mammalian cells (instant claims 41 and 42) as well as bacteria (instant claim 36 since bacteria do not glycosylated expressed proteins). The presence of a secretion leader sequence is taught at column 11, lines 8-9 (instant

claim 43). Pharmaceutical compositions and, by extension, methods of treatment, are taught in claim 15 and at column 1, lines 33-35, for example (instant claims 44-45). They do not teach GLP-1 as the therapeutic protein, nor do they teach the tandem arrangement of multiple copies of the therapeutic protein.

Yamamoto et al. teach recombinant production of desired peptides, particularly when the desired peptide is a relatively low molecular weight peptide composed of less than 100 amino acids (see column 8, lines 21-23), by expressing them as fusions of a proteinaceous carrier (see column 5, lines 55-57) and tandem repeats of desired protein with each repeat preceded by a dipeptide linker (see column 4, lines 40-55. At column 5, lines 10-13 they teach examples of physiologically active peptides including insulin. They do not teach GLP-1 as the desired peptide. They also do not teach albumin as the carrier (although they do teach albumin as a desired peptide at column 7, line 18).

Bridon et al. teach albumin conjugated through its free thiol to an insulinotropic peptide (ITP) derivatized with a maleimide moiety. GLP-1 and its derivatives are named as an ITP and discussed at length at column 4, line 65-column 7, line 17). They do not teach fusion of GLP-1 with albumin, nor, of course, in tandem arrangement. Bridon et al. was chosen as containing representative teachings of GLP-1 derivatives (variants) and Examiner wishes to make it clear that other GLP-1 variants are known, as discussed in the remarks by applicants to the first Office action.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to make fusion proteins between albumin and various therapeutic proteins with the expectation of achieving therapeutic protein having increased serum

half-life as taught by Becquart et al. and Fleer et al. Selection of the N- or C-terminal of the albumin to which to fuse the tandem repeats is well within the ordinary level of skill in the art as shown by the teachings of Fleer et al. in Figures 1A-C. It would have been further obvious to place the multiple copies of therapeutic protein taught by Becquart et al. and Fleer et al. in tandem arrangement as taught by Yamamoto et al. with the expectation of improving the efficiency of expression (see column 8, lines 62-64). Finally, it would have been further obvious to select GLP-1 as the therapeutic peptide in view of the teachings of Bridon et al. of the importance and usefulness of GLP-1 as an insulinotropic peptide – such peptides are well known for treatment of diabetes. One of ordinary skill in the art would know how to decide which variant of albumin or GLP-1 to use; thus, it would have been obvious to select any of them since they are equivalent in this context. Similarly, it is within the ordinary level of skill in the art to determine which of the well-known host cells to use to express the fusion protein since they, too, are equivalent in this context.

Conclusion

9. No claim is allowed. Baggio et al. is cited as of interest.

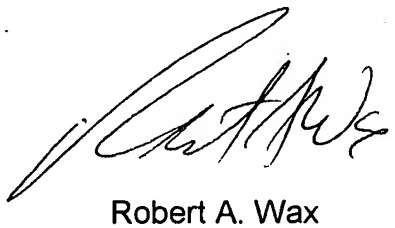
10. Applicant's amendment necessitated the new grounds of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

11. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Robert A. Wax whose telephone number is (571) 272-0623. The examiner can normally be reached on Monday through Friday, between 9:00 AM and 5:30 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jon P. Weber can be reached on (571) 272-0925. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Robert A. Wax
Primary Examiner
Art Unit 1653

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